REMARKS

This Amendment is being submitted in response to the Office Action dated November 15, 2007 in the above-identified application. The due date for filing a response to the November 15, 2007 Office Action is May 15, 2008. A request for extension and payment of the attendant fee are enclosed herewith.

Claims 15-19 have been cancelled and Claims 1, 10, 13, 14, 19, 20, 21, and 31 have been amended for the purpose of expediting prosecution and to narrow the issues in the present application. New claims 41-55 have been added and are supported throughout the specification. Specifically, support for the phrase "in an amount effective to provide" in claim 1 can be found in the language of the claims as filed (e.g., "wherein said beta adrenergic agonist produces an enhanced effect of said analgesic") and in the Specification at, e.g., page 29. Support for the phrase "and combination thereof" in claims 20, 21, 42, and 43 can be found in claim 1 as originally filed. Support for claims 10, 31 and can be found in the Specification on page 17 and in Table 1. Support for claim 14 can be found for example in the Specification on page 11, lines 13-29. Support for claim 19 can be found in the Specification on e.g. page 11, lines 13-29 and on page 17 at line 12. Support for claim 41 can be found in the Specification on page 26, lines 4-7; and support for claims 42 and 43 can be found on pages 20-21. Support for claim 45 and 46 can be found in the first example in the specification, at pages 41-44 and in Tables 3 and 4. Support for claims 47-50 can be found in the Specification in e.g. Table 1. Support for claim 51 can be found in the first example in the specification, at pages 41-44 and in Table 4. Support for claims 52-54 can be found in the Specification at lines 13-17. Support for claim 55 can be found in the Specification on page 23 at lines 13-16.

No new matter has been introduced by the amendments or new claims.

Applicants respectfully request their entry. Claims 1-14, 19-31 and 41-58 are now pending and under examination.

In view of the amendments made herein and the remarks below, Applicants respectfully request reconsideration and withdrawal of the rejections and objections set forth in the November 15, 2007 Office Action.

1. Rejection under 35 U.S.C. Section 112: preventing pain

In the Office Action, the Examiner rejected Claims 1-14, 17 and 20-31 under 35 U.S.C. Section 112, asserting that the specification does not provide enablement for the "prevention of pain".

Applicant respectfully traverses this rejection.

Applicant first points out that for purpose of expediting prosecution and to narrow the issues in the present application, Applicant has amended claim 1 to indicate that the analgesic is an opioid. Applicant therefore is not addressing the issue of enablement for the other analgesics previously listed in Claim 1 at this time.

In her rejection, the Examiner specifically alleges that all of the working examples provided by the specification are directed to the treatment rather than prevention of pain. This is not accurate. In the first example, a mouse is subjected to the tail-flick test after administration of albuterol alone, morphine alone and then administration of both albuterol and morphine. The mouse is not in pain before administration of the active agents. Therefore, this test is as applicable to the prevention of pain, as it is to the treatment of pain. The results of the tail-flick test show an enhanced analgesic effect of morphine in the presence of albuterol. Specification at page 41, lines 2-4. This enhanced effect would be as applicable to the prevention of pain as it is to the treatment of pain.

Further, in various parts of the specification, Applicant specifically discusses appropriate doses of analgesics and of beta adrenergic agonists according to the method

of the present invention (see e.g. Table 1 and Table 2). These dose ranges do not specify prevention versus treatment, indicating that Applicant intended these dose ranges to be used for both for prevention of pain and for the treatment of pain.

Although the Examiner argues that the nature of the invention is complex, Applicant responds that those of skill in the art are well versed in appropriate dosing of the claimed analgesics for the prevention of pain and for the treatment of pain. As for the breadth of the claim, the Examiner seems to argue that because pain has many different causes, the administration of the claimed compounds would not necessarily address all of these different types of pain. The Examiner has cited no support for this statement. If the Examiner means to say that certain pain cannot be prevented, Applicant responds that one of skill in the art would understand the difference between the types of pain that may be prevented and the types of pain that may only be treated (for example, terminal cancer pain that can no longer be prevented).

As for the Examiner's question of "how" one would administer the claimed compounds to a subject in order to actually prevent pain, all the necessary guidance is indeed provided by the specification. The specification clearly sets forth doses for many of the contemplated analgesics and beta adrenergic agonists. One of skill in the art would understand that these doses are applicable to both the prevention and the treatment of pain and would have the necessary skills to understand the proper amounts to use. The specification also explains that administration of the analgesic and beta adrenergic agonist an be via oral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, transmucosal, buccal, inhalation, intranasal, epidural, intrathecal and intraricular, rectal or ocular routes. Specification at Page 26, lines 6-9.

In view of the above, Applicant respectfully submits that the present specification (coupled with guidance available in the art) provides sufficient guidance for one skilled in the art to practice the invention without undue experimentation and requests that the rejection be removed.

2. Rejection under 35 U.S.C. Section 112: enablement beyond morphine and albuterol

In the Office Action, the Examiner rejected Claims 1-14, 17 and 20-31 under 35 U.S.C. Section 112, asserting that the specification is enabling for the "treating pain comprising administering the specific opioid (i.e. morphine) and the specific beta adrenergic agonist (i.e. albuterol), but "does not reasonably provide enablement for "treating pain administering opioids and beta adrenergic agonists".

Applicant respectfully traverses this rejection.

Applicant again points out that for purpose of expediting prosecution and to narrow the issues in the present application, Applicant has amended claim 1 to indicate that the analgesic is an opioid. Applicant therefore is not addressing the issue of enablement for the other analgesics previously listed in Claim 1 at this time.

Applicant respectfully disagrees with the Examiner's analysis and submits that when all the Wands factors are considered together the enablement is shown.

As acknowledged by the Examiner, a synergistic effect has been shown for the combination of morphine and albuterol in the examples. As discussed on Page 44 of the specification regarding the results of the example evaluating synergy between albuterol and morphine and as shown in Table 5 (see page 44), the combination of albuterol and morphine present a synergistic effect. As specifically stated on page 44 of the Specification:

> These dose-response curves were constructed from the linear portions of the effect curves. The enhanced analgesic effect of morphine in the presence of albuterol was synergistic at both time points. The A_{50} value for morphine in the presence of albuterol 30 minutes after injection was 1.50 mg/kg (95% C.I.: 1.26 to 1.77). This represents a significant 3-fold shift to the left of the dose-response curve. Similarly, the A_{50} value of morphine plus

> albuterol 60 minutes after injection was 2.41 mg/kg (95% C.I.: 2.24 to 2.61), representing a significant 4-fold shift to the left of the dose-response curve. If there were no enhanced analgesic effect of morphine in the presence of albuterol, then the A_{50} values of morphine in the presence of albuterol would be the same as those of morphine alone. These results are summarized in Table 5 below. A significant potency ratio is indicated when the confidence intervals of the potency ratio exclude unity (Tallarida and Murray, 1987)...
>
> The data show that albuterol alone has no biologically significant antinociceptive activity. Under the conditions of the experiments, there was a synergistic interaction between albuterol and morphine. Co-administration of albuterol with morphine increased the analgesic potency of morphine 3 to 4 fold.

The claims, as currently amended, are directed to administration of one or more opioids and one or more beta adrenergic agonists in an amount effective to provide an enhanced effect of said opioid(s). Both opioids and beta adrenergic agonists are specific, well-known classes of drugs. In the Specification of the present invention, Applicant discusses these drug classes and explains appropriate dosing of these drugs.

For example, the Specification on page 28, beginning at line 15 explains that, the dose of opioid required in the present invention varies considerably depending on the type of pain (e.g., acute vs. advanced cancer), pain severity, tolerability of side effects, tolerance to analgesic effects, clinician's experience with the analgesic and patient response to treatment. As further explained in the Specification, there are established standards to allow practitioners in the art to convert the dose of one opioid analgesic, given by any route of administration, to an equivalent dose of another opioid analgesic, given by any route of administration. It is Applicant's position that morphine is the well-known standard in the art for the testing of opioids and is commonly used as a representative of the class of opioids in both the prior art literature and in prior art patents. It is respectfully submitted that one of skill in the art would be well used to

working with morphine data to determine appropriate patient dosing with another opioid. Further, the amount of opioid to use for different types of pain is not only within the skill of those in the art and easily found in the prior art literature, but Applicant also gives ample direction in this regard. As evidence, Applicant points to the Specification at page 29 which discusses dosing for a number of exemplary opioids and instructs on opioid dosing for various routes of administration. The Specification at page 29 also instructs on dosing for extended or sustained release formulations. In addition, Table 1 of the Specification details specific dosage ranges for a broad list of opioids and also sets forth appropriate dose ranges of beta adrenergic agonists to be used in combination with the listed opioids. (see Specification at page 31).

As such, it is Applicant's position that enablement of morphine enables the entire class of opioids.

Similarly, it is Applicant's position that albuterol is a well-known beta adrenergic agonist in the art for the testing of beta adrenergic agonists and is commonly used as a representative of this class in the prior art literature and in prior art patents. It is respectfully submitted that one of skill in the art would be well used to working with albuterol data to determine appropriate patient dosing with another drug in the respective beta adrenergic agonist class. Further, Applicant also gives ample direction regarding appropriate dosing of beta adrenergic agonist in the Specification of the present invention. For example, pages 16 to 18 of the Specification discusses preferred beta adrenergic agonists and exemplary dosing. Appropriate dosing pursuant to the present invention is also explained on page 29 of the Specification and is set out in Table 1, located on page 31 of the Specification.

Applicant has given ample direction of how to treat pain by administering one or more opioids and one or more beta adrenergic agonists in an amount effective to provide an enhanced effect of said opioid(s). It is Applicant's position that it would not take undue experimentation for one of skill in the art to make or use the presently claimed

invention and that in many cases, no experimentation at all would be needed. As stated in MPEP Section 2164.06:

> "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 U.S.P.Q. 150, 153 (CCPA 1977). "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (*citing In re Angstadt*, 537 F.2d 489, 502-04, 190 U.S.P.Q. 214, 217-19 (CCPA 1976)).

As for the Examiner's statement regarding prevention of pain, as addressed in detail above, the tail flick test does address prevention of pain as the synergistic combination of morphine and albuterol are administered before the test begins. Moreover, it is respectfully submitted that one of skill in the art would understand and would be well prepared to determine an appropriate dose of each drug, without the need for undue experimentation.

In view of the above, Applicant respectfully asserts that the specification the (coupled with guidance available in the art) provides sufficient guidance for one skilled in the art to practice the invention without undue experimentation and is enabling for the combination of opioids and beta adrenergic agonists. Accordingly, Applicants requests that the Examiner's rejection be withdrawn.

3. Rejection under 35 U.S.C. Section 103

a. Rejection in view of Breton *et al.* and Naftchi *et al.*

The Examiner rejected Claims 1-14, 17, 20-24 and 28-31 35 U.S.C. Section 103(a) as being unpatentable over Breton *et al.* (U.S. Patent No. 5,958,432) and Naftchi

et al. (1981).

According to the Examiner, "the Breton patent teaches that beta-adrenergic agonists including salbutamol, isoproterenol, CGP1217, nylidrin, salmeterol, fenoterol, terbutaline or pirbuterol are substance P antagonists, which are involved in the transmission of pain. (column 2, lines 28-31, and column 1, lines 45-50, column 3, lines 9-15)." The Examiner further asserts that "the Naftchi *et al.* publication suggests that morphine analgesic is due to inhibition of intraneuronal substance P release in regions. (abstract)".

Applicant respectfully traverses this rejection. As explained below, it is Applicant's position that the prior art cited by the Examiner does not teach or suggest the combination of one or more opioids and one or more beta adrenergic agonists. It is Applicant's further position that the prior art does not teach or suggest the beneficial effect obtained from the combination of these two classes of drugs, as demonstrated in the first Example of the Specification. As a result, the combination of these references cannot render the presently claimed invention obvious.

A. The Breton Patent (5,958,432)

The Breton patent, whose assignee is the cosmetics company, L'Oreal, is directed at the use of beta adrenergic agonists for the treatment of cutaneous disorders. It should be noted that the Breton patent does not teach or suggest use of opioids, let alone opioids in combination with beta adrenergic agonist.

It is Applicant's position that the Breton patent erroneously asserts that beta adrenergic agonists are substance P antagonists. The Breton patent provides no scientific evidence in the Specification to support this claim.

Specifically, in the Breton patent, the purported proof of beta adrenergic agonists as substance P antagonists is based solely on the inhibition of tissue permeability

measured indirectly by the extravasation of Evans blue dye. The Evans Blue dye, which was introduced in 1920, is widely used to study in vitro cellular permeability and in vivo vascular leakage. However, it is Applicant's position that inhibition of plasma extravasation as measured by reduction in Evans blue discharge is widely known to be a non-specific test. It is certainly not a direct or specific test of substance P activity. The fact that an established substance P antagonist such as Spantide II reduces plasma or tissue extravasation of Evans blue dye does not, in Applicant's view, provide evidence that beta adrenergic agonist are substance P antagonists. In fact, the Neurosciences publication cited in the Breton patent makes no reference to beta adrenergic agonists or to the use of the Evans blue test as a specific test for substance P activity. See Xu X-J *et al.*, *Spantide II, A Novel Tachykinin Antagonist, and Galanin Inhibit Plasma Extravasation Induced By Antidromic C-Fiber Stimulation In Rat Hindpaw*, Neurosciences, 42(3):731-37 (1991) attached as Exhibit A. A wide variety of agents have been demonstrated to block neurogenic inflammation and its sequelae without having any effect on substance P.

The antidromic stimulation model used by Breton produces multiple biochemical, neuropepetide, membrane and inflammatory perturbations. Beta agonists have a wide variety of pharmacologic effects including reduction in vascular permeability, inhibition of inflammatory mediators, stimulation of ciliary function, modulation of ion and water transport across the mucosa, inhibition of edema formation, smooth muscle relaxation, and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells. Beta agonists have also been shown to inhibit plasma protein extravasation and inhibit platelet-activating factor-induced eosinophil accumulation. Consequently, it is Applicant's position that multiple mechanisms of action can account for its effects in reducing Evans blue dye extravasation following antidromic stimulation.

To Applicant's knowledge, there is no evidence in the prior art to support the view that beta adrenergic agonists are substance P antagonists. However, even if the Breton patent is correct that beta adrenergic agonists are substance P antagonists, this would still not get one of skill in the art any closer to the presently claimed invention. It

is respectfully submitted that it is important to note that substance P antagonists (also known as neurokinin 1 receptor antagonists or NK_1 receptor antagonists) have consistently failed to demonstrate any analgesic efficacy in humans, and, as a result, attempts at developing this class of drugs has now been abandoned by major pharmaceutical companies:

> The long-acting NK_1 receptor antagonist aprepitant was ineffective in postsurgical dental pain following third molar extraction Reinhardt *et al.*, *Comparison of the neurokinin - 1 antagonist, L-754,030, to placebo, acetaminophen and ibuprofen in the dental pain model*, Clinical Pharmacology and Therapeutics, 63:168 (1998). (*See*, Exhibit B)
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> Similarly, the NK_1 receptor antagonist CP-122,721 was ineffective in relieving pain or postsurgical morphine consumption following Abdominal Hysterectomy, Gesztesi *et al.*, *Substance P (Neurokinin-1) Antagonist Prevents Postoperative Vomiting after Abdominal Hysterectomy Procedures*, Anesthesiology 93:931–7 (2000). (*See*, Exhibit C)
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> The NK1 receptor antagonist aprepitant was ineffective in treating pain and central sensitization in the electrical hyperalgesia (neuropathic pain) model in human volunteers. Chizh *et al.*, *Effects of oral pregabalin and aprepitant on pain and central sensitization in the electrical hyperalgesia model in human volunteers*, British Journal of Anaesthesia 98:246–54 (2007). (*See*, Exhibit D)
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> Importantly, unlike pregabalin, the NK1 receptor antagonist aprepitant did not improve the efficacy of the COX-2 selective NSAID parecoxib in treating pain and central sensitization in the electrical hyperalgesia (neuropathic pain) model. In fact, the area of hyperalgesia was somewhat enlarged after aprepitant plus parecoxib vs. placebo plus parecoxib treatment. Chizh *et al.*, *Effects of oral pregabalin and aprepitant on pain and central sensitization in the electrical hyperalgesia model in human volunteers*, British Journal of Anaesthesia, 98:246–54 (2007). (*See*, Exhibit D)

> The NK_1 antagonist lanepitant had no significant beneficial effect on pain intensity when compared with placebo in patients with painful diabetic peripheral neuropathy. Goldstein *et al., Lanepitant, an NK-1 antagonist in painful diabetic neuropathy*, Clinical Pharmacology and Therapeutics, 65:119 (1999) (Abstract PI-8). (*See*, Exhibit E)
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> The NK_1 antagonist lanepitant was also ineffective in patients with moderate to severe pain of osteoarthritis. Goldstein *et al., Lanepitant in osteoarthritis pain", Clinical Pharmacology and Therapeutics* 63:143 (1998). (Abstract PI-24) (*See*, Exhibit F)
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> The NK_1 receptor antagonist GR205171 failed to provide efficacy as abortive treatments for migraine headache. Connor *et al., Clinical evaluation of a novel, potent, CNS penetrating NK_1 receptor antagonist in the acute treatment of migraine* Cephalalgia, 18:392 (1998) (Abstract 9.2). (*See* Exhibit G)
>
> The NK_1 receptor antagonist lanepitant failed to provide efficacy as abortive treatments for migraine headache. Goldstein *et al., Ineffectiveness of neurokinin-1 antagonist in acute migraine: a crossover study*, Cephalalgia, 17:785-790 (1997). (*See,* Exhibit H)
>
> The NK_1 receptor antagonist lanepitant had no effect on migraine frequency and severity when compared to placebo. Goldstein *et al., Lanepitant, an NK1 antagonist, in migraine prophylaxis*, Clinical Pharmacology and Therapeutics, 65:129 (1999). (Abstract PI-8) (*See,* Exhibit I).

These findings are widely accepted in the analgesic drug development and neuroscience community, and in Applicant's opinion, support the view that NK_1 receptor antagonists are not effective as analgesic agents in humans.

Finally, it is worth pointing out that the Breton patent teaches:

> The presence of a substance P antagonist in the form of at least one .beta.-adrenergic agonist in a cosmetic or pharmaceutical composition comprising an active agent

> eliciting an irritant effect makes it possible to greatly reduce or indeed eliminate this irritant effect.
>
> This additionally permits increasing the amount of active principle eliciting an irritant effect with respect to the amount of active principle normally used, for the purpose of improved effectiveness. (emphasis added). Col. 8, ll 38-46.

Thus, the Breton patent teaches that use of beta adrenergic agonists allows for increased amounts of active agents, such as antibacterial agents, antivial agents, anti-inflammatory agents and antiacne agents. It does not discuss this increased amount of active in terms of enhanced effect, but instead teaches that by reducing or eliminating the irritant effect of the active agent, the beta adrenergic agonist allows for use of more active. This is very different from the teaching of the presently claimed invention, the claims of which are directed to administration of one or more opioids and one or more beta adrenergic agonists to provide an enhanced effect of the opioid(s).

B. Naftchi et al, Peptides 1981:2 (suppl. 1): 61-70

The Naftchi *et al.* publication asserts that after pretreatment with morphine, certain regions of the spinal cord show an increase in substance P following spinal transection. Consequently, according to the Naftchi Publication, morphine exerts its analgesic effects through inhibition of substance P release.

As noted above (under our discussion of the Breton patent), it is Applicant's position that even potent and specific substance P antagonists do not produce analgesia in humans. Following morphine administration, there are a wide variety of biochemical and receptor changes in the central and peripheral nervous system. Applicant contends that such changes do not suggest or indicate that morphine or other opioids produce analgesic effects through such changes, which are secondary to morphine administration. In fact, the view that morphine exerts its analgesic effects through inhibition of substance P is not supported by the data or by the current scientific consensus in the analgesic or

neuroscience community. As evidence, Applicant provides herewith two recent state of the art book chapters on opioid pharmacology and opioid mechanisms: (i) Gutstein and Akil, *Opioid Analgesics*, Goodman & Gilman's The Pharmacological Basis of Therapeutics, (Bunton, Lazo and Parker, Eds, 11th Edition 2006). (*See* Exhibit J hereto); and (ii) Dickenson and Kieffer, *Opiates: basic mechanisms,* Wall and Melzack's Textbook of Pain, (McMahon and Koltzenburg, Eds 5th Edition 2005). (*See* Exhibit K hereto).

Indeed, some studies contradict the findings of the Naftchi *et al.* publication (See for e.g., Morton *et al.*, *Morphine and substance P release in the spinal cord,* Experimental Brain Research, 82(1):89-96 (1990). (*See* Exhbit L hereto)

The Naftchi *et al.* publication does not teach or suggest combining morphine or other opioids with any other active agent (other than Naloxone, which was used for testing purposes and is well known to block, not enhance, the effect of morphine). Therefore, the Naftchi *et al.* publication cannot teach or suggest the combination with a beta adrenergic agonist, regardless of whether beta adrenergic agonists are substance P antagonists (and again, Applicant states its opinion that they are not). The Naftchi *et al.* publication therefore cannot teach or suggest the claimed administration of one or more opioids and one or more beta adrenergic agonists to provide an enhanced effect of the opioid(s).

In view of the above, no proper motivation exists for one of skill in the art to combine the Breton patent and the Naftchi *et al.* publication. Further, it is Applicant's position that combination of these references is improper.

As explained above, it is Applicant's position that the Breton patent is in error in finding beta adrenergic agonists to be substance P antagonists. Even if beta adrenergic agonists have such action, the art teaches that substance P's are not effective analgesics. Although it discusses other uses, the Breton patent focuses on treatment of sensitive skin

and is owned by a well known Cosmetic company, L'Oreal. More importantly, the Breton patent does not even teach or suggest the use of opioids and its primary focus is on the decrease of irritant effect of active agents through use of beta adrenergic agonists.

The Naftchi *et al* publication, in contrast, is focused on testing for a purported pathway by which morphine might exert analgesic activity. The Naftchi *et al* publication does not provide *any* causal evidence that opioids exert *analgesia or antinociceptive effects* through substance P antagonism. It is Applicant's position that there is no credible scientific evidence that opioids are substance P antagonists or that opioids exert analgesia by antagonizing substance P. While opioids are effective analgesics, substance P antagonists have repeatedly demonstrated that they are *not analgesic*. And again, the Naftchi publication does not teach combining morphine with any drug beyond naloxone, which antagonizes its effect.

As a result, there would be no motivation for one of skill in the art to combine the Breton patent and the Naftchi *et al.* publication.

Moreover, even if the combination were proper, the Naftchi *et al.* publication does not remedy the deficiencies in the Breton patent. Neither the Breton patent, nor the Naftchi *et al.* publication teach or suggest the combination of opioids and beta adrenergic agonists, let alone teach or suggest that the beta adrenergic agonists might enhance the effect of the opioid (as shown in the first Example of the present specification). It is for this further reason that the combination of these references cannot render the presently claimed invention obvious.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection of the claims as obvious over the Breton patent and the Naftchi *et al.* publication.

b. Rejection in view of Breton et al. and Naftchi *et al.*, in further view of Malmqvist-Granlund *et al.*

The Examiner further rejected Claims 25, 26 and 27 under 35 U.S.C. Section 103(a) as being unpatentable over Breton et al. (U.S. Patent No. 5,958,432) and Naftchi et al. (1981) as applied to claims 1-14, 17, 20-25, and 28-31 above, and further in view of Malmqvist-Granlund et al. (U.S. Patent No. 5,178,868). The Examiner acknowledged that Breton et al. and Naftchi et al. do not teach oral administration, but argued that Malmqvist-Granlund et al. teach that morphine and salbutamol (also known as albuterol) can be formulated as an oral formulation.

For the reasons explained above, Applicant asserts that the combination of the Breton patent and the Naftchi *et al.* publication do not render the present claims obvious. Applicants submit that even if one skilled in the art were to combine the Malmqvist-Granlund patent with these two references, the combination of the references would still not have suggested to the skilled person a synergistic combination of opioids and beta adrenergic agonists.

The Malmqvist-Granlund patent does not teach or suggest the combination of opioid and beta adrenergic agonist claimed in the present invention and indeed, is only cited by the Examiner to show that opioids and beta adrenergic agonists can be formulated into an oral formulation. The Malmqvist-Granlund patent is only directed to a very specific oral formulation. It does not teach or suggest the combination of these different classes of drugs, let alone that the beta adrenergic agonist might enhance the effect of the opioid. Clearly, the Malmqvist-Granlund patent cannot cure the deficiencies of the Breton patent and the Naftchi *et al.* publication.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection of the claims as obvious over the Breton patent and the Naftchi *et al.* publication., in further view of Malmqvist-Granlund *et al.*

c. Rejection in view of Brochet *et al.*

The Examiner rejected Claims 1-14, 17, and 20-31 under 35 U.S.C. Section 103(a) as being unpatentable over Brochet *et al.* (1986). According to the Examiner, Brochet et al. teach antinociceptive activity of beta-adrenoreceptor agonists including isoproterenol, clenbuterol and salbutamol (also known as albuterol on the hot plate test in mice. The Examiner acknowledged, however, that Brochet *et al.* lack opioids, amounts of salbutamol, the oral administration and mechanisms of action set forth in claims 5-8 and 11-13.

Applicant respectfully traverses this rejection. As acknowledged by the Examiner, the Brochet *et al.* publication does not even mention opioids. It is Applicant's position that it therefore cannot possibly teach or suggest the combination of one or more opioids and one or more beta adrenergic agonists. It is Applicant's further position that this publication does not teach or suggest the beneficial effect obtained from the combination of these two classes of drugs, as demonstrated in the first Example of the Specification. As a result, the Brochet *et al.* publication cannot render the presently claimed invention obvious.

The Brochet *et al.* publication asserts that the beta adrenergic agonists, isoproteronol, albuterol (salbutamol) and clenbuterol produce a modest antinociceptive in the rat hot plate model when given intraperitoneally. The magnitude of the purported antinociceptive effect demonstrated in the Brochet publication would not, in Applicant's view, be considered to be of biological significance to one of skill in the art. The results in the Brochet publication are consistent with the data presented by Applicant in the present invention, showing an antinociceptive effect of albuterol which did not rise above 20% MPE (maximum possible effect) over the entire dose-range tested. See Specification at page 41. As stated by Applicant in the Specification:

> Importantly, albuterol given alone produced a minimal antinociceptive effect over the dose range of 0.25 mg/kg to 20 mg/kg. Although the increases in tail-flick latency were

> statistically significant, these increases were only in the order of 1 to 1.2 sec, which is of limited biological significant (sic), and are thus considered inactive (sic) this analysis. Absent any interaction, the dose-effect curves for morphine alone and in the presence of albuterol should be identical. Alternatively, a significant shift to the left of the dose-effect curve for morphine in the presence of albuterol would indicate a synergistic interaction.

The Brochet *et al.* publication does not teach or suggest combining beta adrenergic agonists with any other active agent, let alone with analgesics to obtain additive effects to provide analgesic dose sparing effects or to ameliorate analgesic side effects. The Brochet *et al.* publication certainly does not teach or suggest the administration of one or more opioids and one or more beta adrenergic agonists to provide enhanced effect of the opioid(s) as claimed in the present application. It is respectfully submitted that it is only through hindsight recreation that the Examiner is able to obtain suggestion of the present invention in view of the Brochet *et al.* publication.

There would be no expectation from the teachings found in the Brochet *et al.* publication of the beneficial effect of the combination of opioid and beta adrenergic agonist as demonstrated in the first Example beginning on page 41 of the present Specification. As discussed on page 44 of the specification, the Example showed an "enhanced analgesic effect of morphine in the presence of albuterol that was synergistic at both time points." Synergism is an extremely rare phenomenon that must be documented with appropriate experimental and statistical rigor. Current pharmaceutical understanding does not allow a way to foresee synergism or even simple additivity for drug combinations. This concept is well known and is common knowledge to those skilled in the art of formulation of pharmaceutical compositions. Applicant respectfully submits that analgesic efficacy of combinations of drugs is inherently unpredictable, a fact generally accepted by pharmacologists. Even accepting the Examiner's assertions with respect to the prior art, Applicant respectfully asserts that one of skill in the art

would have no expectation of an enhanced effect from combining beta adrenergic agonists with opioids.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection of the claims as obvious in view of the Brochet *et al.* publication.

CONCLUSION

In view of the amendment set forth herein and remarks above, Applicants respectfully submit that the pending claims are allowable, and solicit the issuance of a notice to such effect. If a telephone interview is deemed to be helpful to expedite the prosecution of the subject application, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number provided.

Respectfully submitted,
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